REMARKS

Claims 1-2 and 28-29 are cancelled herein without prejudice to prosecution in a continuation application. Claims 4 and 32 are amended. New claims 36-40 are added. Thus, claims 4-5, 8, 15, and 30-40 are currently pending in the application.

Applicants wish to thank the Examiner for the courtesy of a telephone interview on May 9, 2003. The finality of the previous Office Action was withdrawn in light of some uncertainty concerning which claims fell under which rejections. The rejection of claim 1 under 35 USC § 103 in view of Carter and Klein was noted as being withdrawn. The analysis of IL-6 as recited in the methods was discussed. It was agreed that Applicants would submit a response that addressed the nonobviousness of the claims over the Klein reference.

Claims 1-2 and 28-29 have been cancelled. Claim 8 has been amended to depend from claim 4 in light of the cancellation of claims 1-2 and the submission of new claim 36. Claim 8 has also been amended to recite that the first bone marrow preparation is a fresh supernatant.

Applicants have amended claims 4 and 32 to more particularly point out and distinctly claim the invention. Claim 4 has been amended to recite that the claim is directed to a method for monitoring the status a multiple myeloma-related plasmaproliferative disorder (MRPD) in an individual diagnosed with such a condition. In claim 4, the amount of IL-6 produced in response to an MRPD marrow sample is compared to the amount of IL-6 produced by stromal cells in response to a normal bone marrow sample. Claim 32 as amended is directed to a method similar to that of claim 4. In claim 32, the amount of IL-6 produced by stromal cells in response to an MRPD bone marrow sample is compared to the IL-6 amount produced in response to 1 pg/ml of IL-1β.

New dependent claim 36 depends from claim 4. New dependent claims 37-38 depend from claim 15. New dependent claims 39-40 depend from claim 32. Each of these dependent claims recites a particular bone marrow preparation.

Support for the claim amendments above is found throughout the specification. No new matter is added by these claim amendments.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1-2 under 35 U.S.C. § 112, first paragraph, as being indefinite. Claims 1-2 have been cancelled without prejudice, thus rendering the rejection moot.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 4, 5, 8 and 30-35 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner asserted that the specification, while enabling for IL-6 production, does not reasonably provide enablement for differentiation between various types of myeloma related plasmaproliferative disorders (MRPD). The Examiner referred to data provided in Figures 4 and 5A-B, and asserted that it is not clear that MRPD can be differentiated from normal. Applicants respectfully traverse.

The specification enables one of ordinary skill to make and use the invention as claimed in amended claims 4-5, 8, 30-36 and 39-40, because the data in Figures 4 and 5A-B show that MRPD conditions can be differentiated. MRPD conditions include MGUS (monoclonal gammopathy of undetermined significance), SMM (smoldering multiple myeloma), and IMM (indolent multiple myeloma).

The data in Figures 4 and 5A-B indicate that IL-6 production in response to bone marrow supernatants from MGUS patients is similar to the IL-6 production in response to bone marrow supernatants from normal patients. The similarity in IL-6 production between MGUS and normal patients is expected because MGUS patients present with different blood or urine chemistry characteristics than do SMM and IMM patients. See, specification at page 7, lines 17-21. SMM and IMM patients, although asymptomatic, have a clinical chemistry profile that raises greater concerns about progression to full-blown multiple myeloma. See page 7, lines 25-29. Clinical chemistry profiles for MGUS, SMM and IMM are summarized in Table 1, at page 8

of the specification. Thus, the data presented in Figures 4 and 5A-B are expected for MGUS patients in light of the inventors' discovery, and teach one of ordinary skill how to make and use the invention with respect to MGUS patients.

IL-6 production in response to bone marrow supernatants from SMM patients can be divided into two types. One type of SMM patient sample induces high levels of IL-6 production, and are at risk of developing multiple myeloma within 1-2 years. Similar results would be expected for IMM patients. See specification at page 18, line 29 to page 19, line 2, and at page 7, lines 28-29. The table below presents data from Figures 4 and 5A-B and show one of ordinary skill how to identify at-risk SMM/IMM patient samples. The data show that IL-6 production in response to media alone, 1 pg/ml IL-1β, the supernatant from a normal patient sample, or supernatants from MGUS patient samples was different from IL-6 production in response to supernatants from at-risk SMM patient samples or supernatants from multiple myeloma patient samples. It is clear that one of ordinary skill can readily differentiate between the large amounts of IL-6 produced in response to at-risk SMM patient samples and the smaller amounts produced in response to 1 pg/ml IL-1β or normal patient samples. The data presented in Figures 4 and 5A-B are expected for SMM/IMM individuals in light of the inventors' discovery, and teach one of ordinary skill how to make and use the invention with respect to SMM and IMM patients.

Sample Type	pg/ml IL-6
Media Only	3,594; 6,676; 4,360
1 pg/ml IL-1β	12,435; 20,199; 17,690.
Normal patient	7,174
MGUS patients	5,546; 7,964; 5,286; 11,811
SMM patients	7,234; 8,263; 6,724; 82,084; 27,975
Multiple Myeloma patients	47,965; 131,512; 92,202; 42,358; 89,058

The Examiner noted that the patient samples were obtained already knowing the MRPD status of each patient, and that the assay is not diagnostic of MRPD condition as such. See Office Action at page 5. The Examiner is correct that the samples were obtained knowing the MRPD diagnosis for each patient. However, the claims are not directed to a diagnostic assay for MRPD. Instead, the claims are directed to a method for monitoring the status of an MRPD patient, and diagnosis is not the intended purpose recited in the pending claims.

The Examiner also referred to "low values" and sample error or variability. Applicants first note that there are no "low values." Figures 4 and 5A-B clearly show that IL-6 values can be measured with commercially available kits. Second, bone marrow preparations from different patients will be expected to vary, of course, because they are obtained from different individuals. However, one of ordinary skill is well aware that assays can be replicated as needed or desired to identify and control for any sample variability that may occur. As evidence of this awareness, a copy of a product datasheet from Biosource International, for product KHC0063, is attached hereto. The Biosource International product datasheet provides the inter-assay coefficient of variation for an IL-6 ELISA kit. An inter-assay coefficient of variation indicates that replicate samples were processed; one of ordinary skill would understand that the claimed methods could be practiced with replicates if needed or desired.

In view of the above, Applicants respectfully request withdrawal of the rejection of claims 4, 5, 8 and 30-35 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 4 and 32 under 35 U.S.C. § 112, second paragraph, as being indefinite with respect to the recitation of IL-6 in the preamble of each claim. Applicants have amended the preamble of claims 4 and 32 to recite monitoring the status of a multiple myeloma-related plasmaproliferative disorder in an individual. Thus, the intended purpose of the method is clear and the recited steps accomplish the intended purpose. The Examiner is requested to withdraw the rejection of claims 4 and 32 under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 103

The Examiner rejected claims 4, 5, 8, 15, 28 and 30-35 under 35 U.S.C. § 103(a) as being unpatentable over Klein et al., Blood, 1989, 73(2):517-526 (hereinafter, Klein). The Examiner asserted that it would have been obvious to one of ordinary skill in the art to monitor IL-6 levels based on the teachings of Klein, especially Figure 1. Applicants respectfully traverse.

Klein measures the presence of IL-6 in supernatants of bone marrow cells from patients with multiple myeloma. See Klein at page 519, left-hand column. Klein reported that patients with fulminating myelomas had higher levels of IL-6 than did patients with inactive/slightly active myeloma. Data for the amount of IL-6 is presented in Figure 1 of Klein. Thus, Klein carries out a direct assay of patient supernatants for IL-6.

The present invention is not a direct assay of patient supernatants for IL-6. Instead, the present invention is an indirect assay of patient supernatants, measuring their ability to stimulate IL-6 production in stromal cells. Klein has no teaching or suggestion whatsoever that samples from individuals with MRPD conditions could or should be monitored by an indirect assay.

Furthermore, a number of references in the prior art taught that IL-6 is not correlated with myeloma disease state. For example, Borset et al. teaches that myeloma cells are not responsible for the overproduction of IL-6. See, e.g., the abstract on page 446, and the third full paragraph on page 449. Kiss et al. failed to observe a correlation between IL-6, IL-1β and myeloma disease state. See, e.g., the abstract and first paragraph on page 335, paragraph 2 on page 337, paragraph 1 on page 338, and paragraph 2 on page 339.

In view of the above, methods as claimed in claims 4, 5, 8, 15 and 30-35 are not taught or suggested in the prior art. Applicants respectfully request that the rejection of claims 4, 5, 8, 15 and 30-35 under 35 U.S.C. § 103(a) be withdrawn.